Harnessing DNA Damage Repair Pathways in Breast Cancer Therapy: a Synthetic Lethality Paradigm

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With more than 200,000 cases reported worldwide in 2012 of which 14,560 from Australia alone, breast cancer is one of the most common malignancies among women. Breast cancer displays highly heterogeneous characteristics. For accurate diagnosis and treatment and also development of effective therapies, breast tumours are morphologically differentiated based on several sub-typing schemes. However, irrespective of the scheme, there is always a subset of tumours that are highly aggressive and do not respond well to traditional therapies.

Modulating DNA damage response (DDR) pathways has shown immense potential as a specialized therapy to counter aggressive tumours, by inducing high levels of DNA damage in cancer cells thereby forcing them into apoptosis while minimizing the impact on surrounding normal-tissue cells. Exploiting *synthetic lethal interactions* has shown some promising results, most notably in BRCA1-deficient cells that are sensitive to PARP inhibition [1,2]. A synthetic lethal relationship between two genes exists when cells remain viable when either or both are normal, but selective killing of cancer cells occurs when both are inactivated. However, except the BRCA1-PARP1 breakthrough few other new synthetic lethal targets have successfully proceeded to clinical trials and been adopted in the treatment of breast tumours.

Here, by combining integrative network-based modelling together with comparative genomic approaches, we seek to identify novel synthetic lethal relationships among components of the DDR machinery that can be effectively translated to treatment of aggressive breast tumours. As a first step towards this goal, through extensive literature searching, we have manually curated DDR pathways to generate a comprehensive and up-to-date map of genes, reactions and mechanisms underlying the DDR machinery. A database of these pathways will be released soon for research purposes. An extensive evaluation of these pathways against known databases and prognostic "gene signatures" for fine-scale sub-typing of breast tumours is currently underway. Furthermore, combining graph-theoretic modelling [3] integrating protein-interaction and gene-expression datasets with comparative genomic approaches [4] for extrapolating synthetic-lethal relationships from lower-order eukaryotes such as yeast, we have identified a subset of drug targets which are now in the pipeline for siRNA-mediated depletion and validation in the lab.

We foresee that our collaborative computational and experimental efforts focused specifically towards identification of synthetic lethal relationships will eventually lead to discovery of specialized drug targets for treating aggressive breast tumours.

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